MR # 312122

SEHSC®
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Via Certified Mail

May 27, 2008

TSCA Document Control Center (7407)
Office of Pollution Prevention and Toxics
US Environmental Protection Agency
Attn: TSCA Section 8(e) Coordinator
Ariel Rios Building
1200 Pennsylvania Avenue, NW
Washington, DC 20004

Re: TSCA Section 8(e) Notification of Substantial Risk: Octamethyltrisiloxane

Dear TSCA Section 8(e) Coordinator:

In accordance with the provisions of Section 8(e) of the Toxic Substances and Control Act (TSCA), as interpreted in the TSCA Section 8(e) Policy Statement and Guidance, Fed. Reg. 33129 (June 3, 2003) and other Agency guidance, the Silicones Environmental, Health and Safety Council (SEHSC)[1] submits, on behalf of its member companies, information concerning an ongoing study with Octamethyltrisiloxane (CAS No. 107-51-7). Neither SEHSC, nor any member company, has made a determination at this time that any significant risk of injury to human health or the environment is presented by these findings

Chemical Substances

107-51-7 Octamethyltrisiloxane

Ongoing Study

Combined Repeated Dose Toxicity Study with Reproductive/Developmental Toxicity Screening Test for Octamethyltrisiloxane (L_3) in Sprague-Dawley Rats via Inhalation Exposure. Dow Corning Study No. 10270-101.

[1] SEHSC is a not-for-profit trade association whose mission is to promote the safe use of silicones through product stewardship and environmental, health, and safety research. The Council is comprised of North American silicone chemical producers and importers.

Contains No CBI CONTAINS NO CBI

Summary

Results from a repeated-dose, subchronic toxicity study with reproductive/developmental screening endpoints conducted with octamethyltrisiloxane (L_3) in Sprague-Dawley rats show test article-related liver effects that include centrilobular hypertrophy (males at 3200ppm, females at ≥800 ppm), protoporphyrinosis (males at ≥ 1600 ppm, not present in females), and increased organ weight (males at 2500 ppm, females at ≥ 800 ppm). There were additional findings that consisted of increased serum levels of cholesterol (males at ≥ 800ppm, females ≥ 1600ppm), slight increase in circulating platelet numbers (males at 3200 ppm), increased incidence of protein droplet nephropathy (males at ≥ 800 ppm, not present in females), and increased incidence of thyroid gland follicular hypertrophy (males and females at 3200 ppm). There were no treatment-related effects on food consumption, body weight, or reproductive/developmental endpoints.

Details

Study Design

In a combined repeated-dose subchronic toxicity study with reproductive/developmental screening endpoints conducted with L_3, male and female Sprague-Dawley rats were exposed to vapor concentrations of 0, 800, 1600, or 3200 ppm L_3 for 6 hr/day for 28 to 42 consecutive days. The study animals were divided into three groups. Group 1 (male toxicity group) consisted of 10 male rats per exposure concentration. Rats in this group were exposed for 29 consecutive days and then euthanized the next day for assessment of toxicity. Group 2 (female toxicity group) consisted of 10 female rats per exposure concentration. Rats in this group were exposed for 28 consecutive days and then euthanized the next day for assessment of toxicity. Group 3 (female reproductive toxicity group) consisted of 10 female rats per exposure concentration. Rats in this group were exposed for 34 – 42 consecutive days. This exposure period included a two-week premating phase, a 1 – 14-day mating phase, and 19 days of gestation. Beginning on study day 14, males from group 1 were paired with females of group 3 from the same exposure concentration after each daily exposure period. Pairing ended when there was positive evidence of copulation. This study design is based on the USEPA OPPTS 870.3650 and OECD 422 test guidelines that include a neurotoxicity screening assessment. A histopathology evaluation was performed on tissues collected for rats in groups 1 and 2.

Results

There were exposure-related microscopic pathology findings observed in the liver, kidney, and thyroid gland. In the liver, there were two independent findings, centrilobular hypertrophy and protoporphyrinosis. Centrilobular hypertrophy, enlargement of hepatocytes in the central part of liver lobules, was observed in males exposed to 3200 ppm and females at every exposure level. Similarly liver weight was increased approximately 14% in males at 3200 ppm and 15, 20, and 27% for females in the 800, 1600, and 3200 ppm exposure groups, respectively.

The second liver finding was hepatic protoporphyrinosis. This lesion was observed only in males at 1600 and 3200 ppm. Under polarized light the material was birefringent, with a highly distinctive pathognomonic appearance that identifies it as protoporphyrin: it appeared bright red

with dark maltese crosses in each globule. The pigment accumulation was accompanied by bile duct proliferation and chronic inflammation.

In the kidney of male rats there was protein droplet nephropathy. In the minimal degree, there were occasional renal proximal tubule cells that contained protein droplets which were angular in shape. At 800 ppm, this was the only indication of an effect. At higher concentrations these crystalline droplet shapes were more common, and the portion of the cortex with visible droplet accumulation increased, along with individual cell necrosis and tubular basophilia. At 3200 ppm, moderate to marked nephropathy was observed in some animals, which included the above changes, as well as granular casts, which are accumulations of necrotic cell debris, at the cortical-medullary border.

The incidence of thyroid gland follicular hypertrophy was increased in males (10% incidence in the control group and 90% incidence in the 3200 ppm group males) and females (20% incidence in control group and 80% incidence in 3200 ppm group females) at the highest exposure concentration.

There were no treatment-related effects on body weight, food consumption, or neurobehavioral (FOB/MA) and reproductive measures. Serum cholesterol levels were elevated in both males (approximately 30% at each exposure level) and females (approximately 30% and 40% at 1600 and 3200 ppm, respectively) as was the concentration of platelets in males at 3200 ppm (increased approximately 20%).

Commentary

The finding of hepatic protoporphyrinosis with L_3 prompted an examination of previously conducted studies on structurally similar siloxane materials. This review identified a finding of hepatic pigment accumulation in males (F_o and F_1) and females (F_1) of a 2-generation reproductive study with hexamethyldisiloxane (HMDS) (Docket # 84060000005). Hepatic pigment accumulation was also identified in males and females of the F_1 generation of a 2-generation reported in a reproductive study with octamethylcyclotetrasiloxane (D_4) (Docket # 88020000003). Although the study pathologists did not term the findings as a protoporphyrinosis the description given is generally consistent with this diagnosis. It is important to note that hepatic pigment accumulation/prophyria and liver tumors have not been observed in the multitude of studies conducted in Fischer 344 rats with these other materials, including 24-month chronic bioassays with both HMDS and D_4. This suggests that expression may be highly dependent on rat strain.

In the light of the findings concerning protoporphyrinosis, a review of the literature was undertaken which identified a number of drugs and some chemicals that can cause this lesion in humans and/or animal models. The significance of hepatic protoporphyrinosis and subsequent tumor formation in animal models with regard to human relevance and risk assessment was recently discussed in a publication by Holsapple and colleagues (Holsapple et al., 2006). This paper summarizes a workshop focused on applying the human relevance framework concept, developed by the International Programme on Chemical Safety and the International Life Sciences Institute's Risk Science Institute, to defining the human relevance of five different modes of action for rodent hepatocarcinogenesis. The working group concluded that

porphyrinogenic compounds have a defined mode of action for inducing hepatocarcinogenesis in rodents involving a threshold and a chronic dose-dependent sustained hepatocellular injury and compensatory hyperplasia. They further concluded that this "cytotoxicity" mode of action should be considered relevant in human cancer risk assessment unless it is known that the underlying mechanism(s) of action giving rise to porphyrinosis in rodents is not relevant to humans.

The observed hepatic protoporphyrinosis occurred only at high inhalation exposure concentrations of 1600 and 3200 ppm for L3, and the reported observation of hepatic pigment occurred only at 1600 and 5000 ppm HMDS, and 300, 500, and 700 ppm D4. These levels are expected to greatly exceed typical workplace and consumer exposures. In addition, the strain specificity of the finding and lack of liver tumors in chronic bioassays with D4 and HMDS may indicate a strain specific mode of action.

Action

SEHSC will provide U.S. EPA with a copy of the final report for this study when it is available.

If you have any questions concerning this submission, please contact me at (703) 788-6570, kthomas@sehsc.com, or at the address provided herein.

Sincerely,

Karluss V. Thomas

Karluss Thomas
Executive Director